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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,835	03/22/2001	Neil Stahl	REG 203B-US	8053

7590 02/08/2005

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EXAMINER	
O HARA, EILEEN B	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 02/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,835	STAHL ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,10-19,25,26 and 29-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,10-19,25,26 and 29-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 November 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-3, 10-19, 25, 26 and 29-35 are pending in the instant application. Claims 1, 26 and 33 have been amended as requested by Applicant in the Paper filed November 10, 2004.

Withdrawn Objections and Rejections

2.1 The rejections of claims under 35 USC § 102 is withdrawn in view of Applicants' arguments.

2.2 Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3.1 Claims 1-3, 10-19, 25, 26 and 29-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sims et al, WO 99/37772, July 29, 1999, and further in view of Lok at al., U.S. Patent No. 5,945,511, filing date Oct. 2, 1997.

Claims 1-3, 10-19, 25, 26 and 29-35 encompass fusion polypeptides comprising a first component comprising an amino acid sequence of an IL-18 binding portion of an extracellular domain of a specificity determining component of an IL-18 receptor, a second component comprising an amino acid sequence of an IL-18 binding portion of an extracellular domain of a signal transducing component of an IL-18 receptor, and a third component comprising the amino acid sequence of a multimerizing component, wherein the multimerizing component comprises an immunoglobulin domain which may be Fc domain of IgG or the heavy chain of IgG, composition capable of binding IL-18 to form a nonfunctional complex comprising a multimer or dimer of the fusion polypeptide, nucleic acids encoding the fusion polypeptides wherein the nucleic acid sequence encoding the first component is upstream or is downstream of the nucleotide sequence encoding the second component, vectors, host cells which may be bacterial, yeast, insect or mammalian, *E. coli*, COS or CHO, recombinant method of making the fusion polypeptide and compositions comprising fusion proteins that bind IL-18.

Sims et al. teaches a fusion heteromeric receptor that binds IL-18. Sims et al. teaches that IL-1Rrp1 binds IL-18 only weakly (specificity determining component of an IL-18 receptor) and mediates signaling in transfected cells and that AcPL (signal transducing component of an IL-18 receptor) does not bind IL-18, but that a complex of IL-1Rrp1 and AcPL results in a dramatic enhancement of signaling in cells stimulated with IL-18 (page 2, lines 10 to 41). Sims et al. teach that dimeric IL-18 receptor complexes comprising IL-1Rrp1 and AcPL or fragments

thereof can be useful for inhibiting IL-18 activity, that AcPL/IL-1RrP1 dimers can be prepared by fusing one of the receptor subunits to the constant region of an immunoglobulin chain and fusing the other receptor to the constant region of an immunoglobulin light chain, and that cells transfected with the DNA encoding these fusion proteins can produce these heterodimers (page 3, lines 1-26). Sims et al. also teaches that IL-1Rrp1 and AcPL receptor subunits may be non-covalently or covalently linked by a polypeptide linker to make fusion proteins, but that for certain applications, e.g. *in vivo* use, covalent linkage is generally preferred in view of the enhanced stability generally conferred by covalent, as opposed to non-covalent, bonds (page 7, lines 34-39). Also taught is that one type of peptide linker that may be employed separates AcPL and the IL-1Rrp1 domains by a distance sufficient to ensure that each domain properly folds into the secondary and tertiary structures necessary for the desired biological activity and the linker should allow the extracellular domains of AcPL and IL-1Rrp1 to assume the proper spatial orientation to form the binding site for IL-18, and that preferably such a fusion protein is prepared by recombinant DNA technology (page 8, lines 4-21). Sims et al. teach that recombinant fusion proteins can be constructed with the C-terminal portion of AcPL fused to the N-terminal portion of IL-1Rrp1, or constructed with the C-terminal portion IL-1Rrp1of fused to the N-terminal portion of AcPL (nucleic acids encoding the fusion polypeptides wherein the nucleic acid sequence encoding the first component is upstream or is downstream of the nucleotide sequence encoding the second component) (pages 11, line 18 to page 12, line 26), expression vectors, host cells which may be bacterial, yeast, insect or mammalian, *E. coli*, COS or CHO, recombinant method of making fusion polypeptides (page 12, line 27 to page 16, line

37), and compositions comprising fusion proteins which are useful as IL-18 binding agents (page 21, line 37 to page 22, line 39, also see claims).

While Sims et al. teaches IL-1Rrp and AcPL each fused to an IgG individually which then combine to form a heterodimeric dimer, Sims et al. does not specifically teach a fusion protein comprising both IL-1Rrp1 and AcPL receptor subunits fused to a multimerizing component which may be Fc domain of IgG or the heavy chain of IgG.

Lok et al. discloses a cytokine receptor identified as Zcytor7, and teaches that receptor extracellular domain can be expressed as a fusion with immunoglobulin heavy chain constant regions, typically an Fc fragment, which are secreted as multimeric molecules wherein the Fc portions are disulfide bonded to each other and two receptor polypeptides are arrayed in close proximity to each other. Lok et al. teaches that fusions of this type can be used to affinity purify the cognate ligand from solution, as an *in vitro* assay tool, to block signals *in vitro* by specifically titrating out ligand, and that chimeras with high binding affinity could be used as antagonists *in vivo* by administering them parenterally to bind circulating ligand and clear it from the circulation.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use Sims et al.'s AcPL/IL-1Rrp1 fusion protein in constructing another fusion protein also comprising a multimerizing domain such as Fc of IgG, as taught by Lok et al., in order to produce a potent IL-18 binding protein, which could be a more effective antagonist of IL-18 than the AcPL/IL-1Rrp1 fusion protein alone. The skilled artisan would be motivated to do so in order to produce a fusion protein comprising at least two IL-18 binding sites as apposed to the single IL-18 binding site of Sims et al., which would be an effective

therapeutic agent that could antagonize the activity of IL-18, which would be desirable, as taught by Sims et al. There would be a reasonable expectation of success, since making fusion proteins using multimerizing components such as the Fc domain has been widely and successfully accomplished, and such fusion proteins have been shown to be effective therapeutic agents, such as etanercept, for example (etanercept (Enbrel.RTM. sold by the Immunex Corporation), which is a recombinant fusion protein consisting of two soluble TNF receptors joined by the Fc fragment of a human IgGI molecule, for treating RA, Juvenile Rheumatoid Arthritis and Psoriatic Arthritis).

3.2 Claims 1-3, 10-19, 25, 26 and 29-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sims et al., U.S. Patent No. 6,589,764, effective priority date January 22, 1999 (previously cited), and further in view of Lok at al., U.S. Patent No: 5,945,511, filing date Oct. 2, 1997.

Sims et al. teaches a fusion heteromeric receptor that binds IL-18. Sims et al. teaches that IL-1Rrp1 (specificity determining component of an IL-18 receptor) binds IL-18 only weakly and mediates signaling in transfected cells and that AcPL (signal transducing component of an IL-18 receptor) does not bind IL-18, but that a complex of IL-1Rrp1 and AcPL results in a dramatic enhancement of signaling in cells stimulated with IL-18 (column 2, lines 32-41). Sims et al. teach that dimeric IL-18 receptor complexes comprising IL-1Rrp1 and AcPL or fragments thereof can be useful for inhibiting IL-18 activity, that AcPL/IL-1RrP1 dimers can be prepared by fusing one of the receptor subunits to the constant region of an immunoglobulin chain and fusing the other receptor to the constant region of an immunoglobulin light chain, and that cells transfected with the DNA encoding these fusion proteins can produce these heterodimers

(column 2, line 10 to column 4, line 11). Sims et al. also teaches that IL-1Rrp1 and AcPL receptor subunits may be non-covalently or covalently linked by a polypeptide linker to make fusion proteins, but that for certain applications, e.g. *in vivo* use, covalent linkage is generally preferred in view of the enhanced stability generally conferred by covalent, as opposed to non-covalent, bonds (column 6 lines 34-42). Also taught is that one type of peptide linker that may be employed separates AcPL and the IL-1Rrp1 domains by a distance sufficient to ensure that each domain properly folds into the secondary and tertiary structures necessary for the desired biological activity and the linker should allow the extracellular domains of AcPL and IL-1Rrp1 to assume the proper spatial orientation to form the binding site for IL-18, and that preferably such a fusion protein is prepared by recombinant DNA technology (column 6, line 51 to column 7, line 4). Sims et al. teach that recombinant fusion proteins can be constructed with the C-terminal portion of AcPL fused to the N-terminal portion of IL-1Rrp1, or constructed with the C-terminal portion IL-1Rrp1of fused to the N-terminal portion of AcPL (nucleic acids encoding the fusion polypeptides wherein the nucleic acid sequence encoding the first component is upstream or is downstream of the nucleotide sequence encoding the second component) (column 9, lines 25 to 43), expression vectors, host cells which may be bacterial, yeast, insect or mammalian, *E. coli*, COS or CHO, recombinant method of making fusion polypeptides (column 9, line 44 to column 14 line 51), and compositions comprising fusion proteins which are useful as IL-18 binding agents (column 17, line 46 to column 18, line 55, also see claims).

While Sims et al. teaches IL-1Rrp and AcPL each fused to an IgG individually which then combine to form a heterodimeric dimer, Sims et al. does not specifically teach a fusion

protein comprising both IL-1Rrp1 and AcPL receptor subunits fused to a multimerizing component which may be Fc domain of IgG or the heavy chain of IgG.

Lok et al. discloses a cytokine receptor identified as Zcytor7, and teaches that receptor extracellular domain can be epressed as a fusion with immunoglobulin heavy chain constant regions, typically an Fc fragment, which are secreted as multimeric molecules wherein the Fc portions are disulfide bonded to each other and two receptor polypeptides are arrayed in close proximity to each other. Lok et al. teaches that fusions of this type can be used to affinity purify the cognate ligand from solution, as an *in vitro* assay tool, and that chimeras with high binding affinity could be used as antagonists *in vivo* by administering them parenterally to bind circulating ligand and clear it from the circulation.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use Sims et al.'s AcPL/IL-1Rrp1 fusion protein in constructing another fusion protein also comprising a multimerizing domain such as Fc of IgG, as taught by Lok et al., in order to produce a potent IL-18 binding protein, which could be a more effective antagonist of IL-18 than the AcPL/IL-1Rrp1 fusion protein alone. The skilled artisan would be motivated to do so in order to produce a fusion protein comprising at least two IL-18 binding sites as apposed to the single IL-18 binding site of Sims et al., which would be an effective therapeutic agent that could antagonize the activity of IL-18, which would be desirable, as taught by Sims et al. There would be a reasonable expectation of success, since making fusion proteins using multimerizing components such as the Fc domain has been widely and successfully accomplished, and such fusion proteins have been shown to be effective therapeutic agents, such as etanercept, for example (etanercept (Enbrel.RTM. sold by the Immunex Corporation), which

is a recombinant fusion protein consisting of two soluble TNF receptors joined by the Fc fragment of a human IgGI molecule, for treating RA, Juvenile Rheumatoid Arthritis and Psoriatic Arthritis).

Conclusion

4. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (571) 272-0829.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to

the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

EILEEN B. O'HARA
PATENT EXAMINER